DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Cincinnati District Office
Central Region
6751 Steger Drive
Cincinnati, OH 45237-3097
Telephone: (513) 679-2700
FAX: (513) 679-2771

January 11, 2007

WARNING LETTER
CIN-07-30670-09

VIA FEDERAL EXPRESS

Joel F. Germunder
President and CEO
Omnicare, Inc.
1600 RiverCenter II
100 East RiverCenter Blvd.
Covington, KY 41011

Dear Mr. Germunder:

An inspection of your drug repackaging facility, Heartland Repack Services LLC, located at 4755 South Avenue, Toledo, OH 43615, was conducted on June 27-August 11, 2006. Drugs repackaged by Heartland Repack Services are distributed through pharmacy services to Omnicare nursing homes, assisted living, and other institutional facilities which according to your website serve more than 1.4 million residents in 47 states and Canada. During the inspection our Investigator documented serious deviations from the Current Good Manufacturing Practice (CGMP) regulations, as set forth in Title 21 of the Code of Federal Regulations (CFR), Parts 210 and 211. These deviations cause your drug products to be adulterated within the meaning of section 501(a)(2)(B) [21 U.S.C. § 351(a)(2)(B)] of the Federal Food, Drug, and Cosmetic Act (the Act).

We acknowledge your firm's corrective action plans, including the recall of all affected products, closing your facility for an extended period of time in order to implement corrective actions, and hiring outside consultants. However, this Warning Letter is being issued because your corrective actions have not yet been completed, and because of your firm's compliance history (including inspections in 1996, 1997, 2004, and 2006 that documented CGMP deficiencies and multiple recalls resulting from poor CGMP controls), the serious nature of the observed violations, and the significant risk to consumers associated with the CGMP deviations involving potential product contamination and product mix-up. Due to the large number of significant deficiencies cited, we thought it would be useful to group the observations in a systematic approach.

The CGMP deviations observed during the inspection include, but are not limited to the following:

FACILITIES

1) **Separate or defined areas or other control systems to prevent contamination or mixup are inadequate, and operations relating to the repacking of penicillin are not performed in facilities separate from those used for non-penicillin drug products for human use. [21 CFR § 211.42(c) and (d)]** Specifically, your firm, which repacks human drugs, shares a building with a pharmacy that packs beta-lactam antibiotics, including penicillins and cephalosporins. Your facility shares a common dock area, common receiving area, doorways, an overhead door near the maintenance room, cleaning equipment, and personnel with the pharmacy. The pharmacy uses the common area to receive beta-lactams. Sufficient controls have not been established to prevent the exposure of cephalosporin drug products and non-beta-lactam drug products to cross-contamination, either with penicillin drug products or with each other.

   In addition, containment procedures have not been established to assure that employees, in moving about the plant, do not carry residue from penicillin into non-penicillin areas or non-penicillin beta-lactams (e.g., cephalosporin) into non-beta-lactam areas. Cephalosporin products, like penicillin products, are categorized as beta-lactam drugs and present a health hazard to consumers with sensitivities to these compounds. Consequently, under 21 CFR 211.42(c), the processing of non-penicillin beta-lactam drugs (e.g., cephalosporin) should be separate from other drug products. Pursuant to 21 CFR 211.42(d), penicillin drug products must also be separate from other drug products, including non-penicillin beta-lactams.

   We recommend a system-based approach that involves a complete separation of every aspect of the repackaging operation. Adequate separation should include physical barriers, air handling systems, personnel, and equipment with well established written procedures and controls. The separation should be verified by testing, auditing, and continuous monitoring if necessary.

2) **Air-handling systems for the packing of penicillin are not completely separate from those for other drug products for human use. [21 CFR § 211.46(d)]** The pharmacy and the repacking operations share a common air handling system, including common air returns, vents, and air sources. This air handling system uses nearly 100% recirculated air.

3) **Separate or defined areas for the storage of in-process materials are inadequate to prevent contamination or mix-ups. [21 CFR § 211.42(c)(4)]** Your firm routinely stages multiple drug products and/or the same drug products with different lot numbers that are released to be repacked in the same storage bin areas. We observed product bins with multiple drug products in the same bin with no spatial separation, the same bin number in multiple locations throughout the warehouse, product stored in aisles between bins due to the unavailability of bins, and a storage rack in the warehouse area with multiple drug products identified for different purposes (e.g., stability samples, rework product, return to stock, and scrap product).

Furthermore, bulk bottles of tablets of the same drug in different strengths were stored immediately adjacent to each other. This allowed for product mix-up in the raw material storage area, resulting in a product mix-up on the repackaging line where digoxin 0.125 mg tablets were included in the repackaging of digoxin 0.25 mg tablets.

EQUIPMENT

4) **Equipment used in the manufacture, processing, packing or holding of drug products is not of appropriate design to facilitate operations for its intended use and for its cleaning and maintenance. [21 CFR § 211.63]** For example, CP-2 packaging line was modified in a manner that made it difficult for employees to remove the line cover. As a result, the line cover is not removed during line clearance operations and is only removed during preventative maintenance. Per firm personnel, unit dose strips can become caught in this area and are routinely found during maintenance.

5) **Routine calibration, inspection, and checking of automatic, mechanical, and electronic equipment are not performed according to a written program designed to assure proper performance. [21 CFR § 211.68(a)]** Review of the service records from June 2005 - July 2006 for the CP-2 packaging line revealed that there were no records for any preventative maintenance from February 2006 - June 2006. In addition, the cleaning procedures for that line states that routine maintenance will be performed during or prior to the cleaning approval as appropriate. The procedure does not include a maintenance interval for the equipment; however, according to the Maintenance Manager, the routine preventative maintenance on the CP-2 packaging line should be done on a monthly interval. An example of this untimely maintenance of equipment is a slit (cut) on the exit belt on the CP-2 packaging line that our Investigators observed during the inspection.

PACKAGING AND LABELING

6) **Failure to establish and follow written procedures designed to assure that correct labels, labeling, and packaging materials are used for drug products, including procedures to prevent mix-ups and cross-contamination by physical or spatial separation from operations on other drug products. [21 CFR § 211.130(a)]** For example, the batch records showed that Thiothixene 5 mg capsules were packaged on the same line at the same time as Metformin ER 500 mg tablets. In your written response, dated August 28, 2006, you surmised that the line clearance was not completed for Thiothixene in its entirety before the Metformin was introduced to the packaging line.

Therefore, both products were on the packaging line simultaneously which resulted in a mix-up of the product lots. Both lots were distributed. On June 22, 2006, customer complaint #060065, was filed which stated that a box of Thiothixene 5 mg contained strips of Metformin ER 500 mg. Both product lots were ultimately recalled.

7) **Strict control is not exercised over labeling issued for use in drug product labeling operations. [21 CFR § 211.125(a)]** Label reconciliation is not fully conducted for pre-

printed roll labeling stock used to label repackaged drug products. The label reconciliation does not include a count of the amount of labels on the roll or reconciliation of the initial number of labels on a roll minus the final amount used. Pursuant to 21 CFR § 211.125(c), label reconciliation is required since your firm does not perform a 100% label examination for correct labeling in accordance with 21 CFR § 211.122(g)(2).

8) **Procedures describing in sufficient detail the control procedures employed for the issuance of labeling are inadequate. [21 CFR § 211.125(f)]** Specifically, two written procedures covering packaging controls do not indicate what is to be done with excess box labels at the end of a boxing run.

Testing and Inspection

9) **Non-penicillin drug products were not tested for the presence of penicillin, when a reasonable possibility existed that a non-penicillin drug product had been exposed to cross-contamination with penicillin. [21 CFR § 211.176]** Specifically, your firm has not tested any of the human drug products that have been repacked by your firm for the presence of penicillin. As pointed out in items 1) and 2) above, your firm does not have separate facilities nor do you have separate air handling systems for handling penicillin products. Your firm shares the building, a common dock area, common receiving area, doorways, an overhead door near the maintenance room, cleaning equipment, personnel, and an air handling system with a pharmacy that packs beta-lactam antibiotics, including penicillins and cephalosporins.

10) **Drug products failing to meet established specifications and quality control criteria are not rejected. [21 CFR § 211.165(f)]** At least two lots of product failed quality control testing limits for a number of sample rejects yet these lots were not rejected and were released for shipment. In the case of Metoclopramide 5 mg tablets, lot C41955A, a total of 80 rejects (crushed tablets) out of a sample size of 80 units was found. For Fexofenadine 60mg tablet Lot #K43240, quality control testing showed a total of 14 rejects out of a sample size of 125 units sampled. These lots of Metoclopramide 5mg tablets and Fexofenadine 60mg tablets should have been rejected according to your firm's written procedures, "Quality Assurance Release of Product for Further Processing or Distribution."

11) **Inspection of the packaging and labeling facilities is not done immediately before use to assure that all drug products have been removed from previous operations. [21 CFR § 211.130(e)]** Specifically, the inspection and line clearance before use on the CP-2 line was not properly conducted between the repackaging of different drug products, resulting in product mix-ups on at least 5 different occasions.

12) **Representative samples of units were not collected and visually examined for correct labeling at the completion of finishing operations. [21 CFR § 211.134(b)]** Drug products packaged on the CP-400 line are not always inspected to assure that all labeling conforms to the labeling specified in the batch production record. For example, the label on the outer carton for Carbidopa/Levodopa 25 mg/100 mg was labeled with the wrong strength (25 mg/250 mg instead of 25mg/100 mg). There are no records that show that the

labeling was inspected after the repackaging run to determine its conformance. This lot was partially distributed.

QUALITY SYSTEMS

13) **The failure to thoroughly investigate and document any unexplained discrepancy or the failure of a batch or any of its components to meet any of its specifications, whether or not the batch has already been distributed. [21 CFR § 211.192]**

a) Specifically, a review of 64 batch production records from January 1, 2006 - July 2006 found: 1 batch for which QC sample defect limits were exceeded and the lot was released; 17 batches for which records contained errors in finished product sampling; 2 batches for which sampling results were not recorded; 3 batches for which records did not identify the type of product defects found; 2 batch records did not contain representative immediate product labeling; 1 batch record did not contain a representative stick-on box label; and 1 batch record for which quality control did not sign the quality control sampling record.

b) Investigations are not always documented when a batch is placed "On Hold" by the quality control unit. The on-hold log is the only record that is maintained of investigations made due to unexplained discrepancies or the failure of the batch or components to meet specifications. The on-hold log is not reliably completed for all batch failures and does not include the outcome of an investigation including its conclusion. In addition, the batch records do not include any investigations that were conducted on the batch.

c) Drug product production and control records are not reviewed and approved by the quality control unit to determine compliance with all established, approved written procedures before a batch is released or distributed. Specifically, at least two batch production records did not contain a quality control batch release signature prior to release of the drug products.

14) **Procedures describing the handling of all written and oral complaints regarding a drug product are not followed. [21 CFR § 211.198(a)]** Your written "Complaint Handling" procedure states that all inquiries meeting the definition of a complaint are to be forwarded to the Quality Assurance Manager for determination as to whether the drug product failed to meet its specifications and an investigation is necessary. Review of the complaint database from July 2005 - July 2006 found approximately 95 records that met the definition of a complaint that were not forwarded for evaluation.

15) **Employees engaged in the processing and packing of a drug product lack the education, training, and experience to enable them to perform their assigned functions. [21 CFR § 211.25(a)]** Specifically, a video recording showing repackaging operations on the CP-2 packaging line showed that employees were not removing unit dose strips of drug product remaining in the equipment or that had fallen to the floor, and that line clearance verification was not performed between uses. Review of the training records

for [redacted] current temporary employees in the production area found: (a) no evidence that any of the employees had been provided with the "Job Duties" form that describes the duties of the operations they are to perform; and (b) the "Temporary Employee Orientation and Training Record" for [redacted] of the employees lacked a date to show that the employee received the training prior to performing the operations covered by the training, and all [redacted] of the employee records lacked the "Supervisor Signature" to show that the training was given.

16) **Batch production and control records are deficient in that they a) do not include documentation of batch investigations performed [21 CFR § 211.188(b)(12)]; and b) do not include the identification of the persons performing, directly supervising, and checking each significant step in the operation, for each batch of drug product produced. [21 CFR § 211.188(b)(11)].** For example, for b), the number of employees present for a boxing run is recorded in the batch record for the run, and the initials of the employees are recorded in the equipment usage log entry for the run. At least two batch records showed inconsistencies in these records regarding who was present and there is no record to identify the individuals represented by these initials. When questioned, no one at Heartland Repack Service was able to name the individuals these initials represent.

All of the above deficiencies are indicative of the failure to have an adequate quality control unit that has the responsibility and authority (among other things) to approve or reject all components, in-process materials, and drug products, to review production records to assure that no errors have occurred or, if errors have occurred, that they have been fully investigated, and to approve or reject all procedures or specifications impacting on the identity, strength, quality, and purity of the drug products [21 CF CFR § 211.22]. The deficiencies in your quality control systems were serious. We remain concerned about the quality control systems and procedural problems that have allowed these significant deficiencies to remain unresolved for so long. In addition, many of these deficiencies were shown to have directly contributed to drug and labeling mix-ups. Failure to adhere to CGMPs could potentially affect the approximately 1.4 million nursing home and healthcare patients who receive drug products repackaged by your firm.

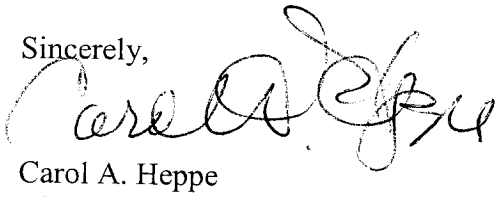
It is important to note that the above identified violations are not intended to be an all-inclusive list of deficiencies at your facility. It is your responsibility to correct these deficiencies and to ensure that your drug repackaging operations are in full compliance with the current Good Manufacturing Practice Regulations and with the Act. Federal agencies are advised of the issuance of all Warning Letters about drug products so that they may take this information into account when considering the award of contracts. Until FDA confirms correction of the deficiencies observed during the most recent inspection, this office can recommend disapproval of any new applications listing this site as a manufacturer of drugs. You should take prompt action to complete corrective actions at your facility. Failure to do so may result in further regulatory action without notice. These actions may include seizure of your products or injunction. As previously stated, this Warning Letter is being issued because actions to correct the CGMP deficiencies identified above have not yet been completed, and because of your firm's compliance history, the serious nature of the observed violations and the significant risk

associated with the product and label mix-ups. Your firm's compliance history includes inspections in 1996, 1997, 2004, and 2006 that documented CGMP deficiencies. Your firm has recalled products due to mislabeling in 1997, 2004, and 2006. There were seven recalls due to mislabeling since June 2006. The latest recall, initiated on August 1, 2006, was due to unacceptable CGMP controls that lead to the possible mislabeling of all drug products within expiry repacked on Klockner CP-2 packaging line. The recall involves 382 drug products that constitute approximately 4,000 different product lots.

We received the response to the FDA-483 Inspectional Observations that was sent by Glen Laschober, Chief Operating Officer, Omnicare, Inc., on August 28, 2006. Your corrective action plan was again discussed during a meeting with your corporate officials at our office on August 30, 2006. We acknowledge your commitments to take specific steps to both correct the noted deficiencies, and to make systemic corrections to assure that similar violations will not recur. We also acknowledge the corrective actions promised by your firm, which include: (1) ceasing production of all products on July 27, 2006, and placing all products in quarantine that are under Heartland Repack Services' control; (2) recalling all marketed product still within expiry date from the suspect packaging line; (3) performing a risk assessment on existing stock; (4) hiring outside consultants to re-evaluate CGMP controls and retrain employees on CGMPs; (5) initiating a penicillin sampling program with environmental swabs and product testing and ceasing all distribution of products until testing is complete; (6) discontinuing use of temporary service employees; (7) hiring new experienced QC/QA and Plant Managers; (8) permanently moving your drug repackaging operation to a new facility; and (9) evaluating all equipment for decontamination procedures and if not feasible, replacing the equipment.

You should notify this office within 15 working days of receipt of this letter of other corrective actions you have not previously included in your written responses, and any additional steps you have taken to correct the noted violations, including the dates the corrective actions were completed and proposed timeframes for completion of each remaining corrective action. If you decide to repack beta-lactam products let us know 1) when you will resume repackaging operations and 2) what type of procedures you will establish to ensure appropriate containment of these products. In addition, please state the reason for any delays in implementing the corrective actions along with the time frames within which corrective actions will be completed. We will review and evaluate the implementation and adequacy of your corrective actions during our follow-up inspection of your firm. Your response should be addressed to: U.S. Food & Drug Administration, 6751 Steger Drive, Cincinnati, OH 45237, Attn: Charles S. Price, Compliance Officer. If you have any questions, you may address them to Mr. Price at (513) 679-2700 extension 165.

Sincerely,



Carol A. Heppe
District Director
Cincinnati District

Cc: Denis R. Holmes, VP Operations Group